

AMENDMENTS TO THE SPECIFICATION

Please add the following paragraph after the Title on page 1:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application Serial No. 09/924,709 filed August 8, 2001, which is hereby incorporated by reference in its entirety.

Please replace the paragraph at page 17, line 23 with the following amended paragraph:

A compound of formula XV, wherein B, X, R, R1 and R2 are as defined above, and A is NH, in turn, can be obtained by reacting a compound of formula XIII, as defined above, with a compound of formula XVI, as defined above, followed by: a) reduction of the nitro group, b) reaction with a compound of formula V, as defined above, c) reduction of the resulting compound with an alkali metal borohydride or an alkali metal [[cyanoborohydride]] cyanoborohydride, d) removal of the [[protectin]] protecting group Z₃.

Please replace the paragraph at page 47, line 4 with the following amended paragraph:

To a suspension of CuI in dry tetrahydrofuran under argon are added 1.1 equivalents of tetramethylene diamine and the reaction mixture stirred at room temperature for 15 minutes. The solution is cooled to -78°C and the Grignard reagent prepared from 7-bromomethyl-4-*p*-methoxybenzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine is added and the reaction mixture stirred for 15 minutes. Then, 2 equivalents of trimethylsilyl chloride and a solution of ethyl cinnamate in tetrahydrofuran are added and the [[reactoin]] reaction mixture is stirred while the temperature is allowed to rise to -30°C. After 18 hours the reaction is poured into a solution of ammonium chloride and ammonium [[hydroxyde]] hydroxide and extracted with dichloromethane. The extracts are washed with water, dried over sodium sulfate, evaporated and the product isolated by flash chromatography.

Please replace the paragraph at page 51, line 7 with the following amended paragraph:

A solid phase assay for the study of $\alpha_{IIb}\beta_3$ - fibrinogen binding was set up according to the method described for $\alpha_v\beta_3$. $\alpha_{IIb}\beta_3$ integrin was diluted into coating buffer (CB) containing 150 mM NaCl, 1 mM CaCl_2 , 1 mM MgCl_2 , 1 mM MnCl_2 , 20 mM TRIS, pH 7.4 at a concentration of 3 $\mu\text{g/ml}$. Into 96-well plates, 50 μl of the diluted integrin were added and allowed to bind to the plate walls overnight at 4°C. Next day, the assay plates were emptied and 100 μl of blocking buffer (CB buffer with 3% BSA) were added to each well for 45 min at 37°C. After the incubation, the plates were washed three times with 100 μl assay buffer (AB, CB buffer with 0.1% BSA); serial 1:1 dilution (25 $\mu\text{l/well}$) of the test compounds were added to the plates, starting from 10 mM solutions in 100% DMSO diluted to 100 μM in AB. The binding reaction was started by addition (25 $\mu\text{l/well}$) of 20 nM biotinylated fibrinogen (final concentration: 10 nM), and lasted 30 min at 37°C. The concentration range of the tested compounds spanned from 50 to 0.0005 μM . At the end of the co-incubation, the assay plates were washed as before and 70 μl of a 1:1000 AB dilution of peroxidase-conjugated streptavidin were added per well and were allowed to react for 45 min at 37°C. Then, the plates were washed as described and 50 μl of ready to use Turbo-TMB substrate for peroxidase were added to each well. After 30 minutes incubation at room temperature, the color development was stopped with 50 μl sulphuric acid 0.38 M and the plates were read at a wavelength of 450 nm with a Packard plate reader. The values obtained were analyzed by four parameters curve fit with the computer program GraphPad Prism, after normalization by a maximum binding control (B_{max}) detected in wells where no competitor was added, and a minimum binding control (NSB) detected in wells where no integrin was coated. Under standard assay conditions, A_{450} was never under 0.8 for B_{max} , and around 0.15 for NSB. The computerized algorithm gave the concentration of compound needed to inhibit the maximum binding by 50% (IC_{50} value): for those compounds that did not inhibit this binding by 50% at the highest concentration tested, IC_{50} value was reported as being greater than the highest concentration tested. As a

positive control, increasing doses of a peptide containing the RGD sequence was added to each plate: IC₅₀ value of this molecule was 2.3 μM for α_{IIb}β₃- fibrinogen binding.

Please replace the paragraph at page 57, line 28 with the following amended paragraph:

The object of the present invention is to provide the use of a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament having $[\square_v\square_3]$ α_vβ₃ integrin inhibiting or antagonizing activity for controlling the growth of the neoplasm in a method additionally comprising the administration of an antitumor agent.